

Increased risk of sudden and non-sudden cardiovascular death in patients with atrial fibrillation/flutter following acute myocardial infarction

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Aims Atrial fibrillation (AF) is a common complication in patients with acute myocardial infarction and is associated with an increase in the risk of death. The excess mortality associated with AF complicating acute myocardial infarction has not been studied in detail. Observations indicate that AF facilitates induction of ventricular arrhythmias, which may increase the risk of sudden cardiovascular death (SCD). A close examination of the mode of death could potentially provide useful knowledge to guide further investigations and treatments.

Methods and results We analysed the relation between AF/atrial flutter (AFL) and modes of death in 5983 consecutive patients discharged alive after an acute myocardial infarction screened in the TRAndolapril Cardiac Evaluation registry. This cohort of patients with an enzyme-verified acute myocardial infarction was admitted to 27 centres in 1990–92. Survival status was obtained 2 years after screening of the last patient. An independent endpoint committee assessed the modes of death. Left ventricular ejection fraction was determined in all the screened patients and information about presence or absence of AF/AFL was prospectively collected. Sustained or paroxysmal AF/AFL was observed in 1149 patients (19%) during hospitalization. During follow-up, 1659 patients (34%) died: 482 (50%) patients with AF/AFL and 1177 (30%) patients without AF/AFL, $P < 0.001$. SCD occurred in 536, non-SCD occurred in 725, and 398 died of non-cardiovascular causes (includes 142 unclassifiable cases). The adjusted risk ratio of AF/AFL for total mortality was 1.33 (95% CI: 1.19–1.49; $P < 0.0001$) and the risk ratio for SCD was 1.31 (95% CI: 1.07–1.60; $P < 0.009$). The adjusted risk ratio of AF/AFL for non-SCD was 1.43 (95% CI: 1.21–1.70; $P < 0.0001$).

Conclusion The excess mortality observed in patients with AF/AFL following acute myocardial infarction is due to a significant increase in both SCD and non-SCD.

Introduction

Atrial fibrillation (AF) is the most frequently encountered cardiac arrhythmia in clinical practice and is associated with an increase in the risk of death in subjects with and without structural heart disease.¹ Whether or not AF is accordingly associated with an increase in the risk of sudden cardiovascular death (SCD) remains controversial. A study of patients with severe heart failure indicates that AF is associated with an increase in the risk of SCD,² whereas Carson *et al.*³ reported no increase in SCD in patients with mild-to-moderate heart failure. The Framingham study demonstrated that AF is an important

risk factor for premature death in the general population¹ and suggested that AF increases the probability of death without changing the mode of death. However, in this study, the mode of death was not examined in detail. So far, no previous study has examined whether there is an association between AF and SCD in patients with myocardial infarction. A closer examination of the mode of death could provide important information to guide further investigations and suggest relevant interventions.⁴ In patients who survive a myocardial infarction, the prevalence of AF is high (up to 20%)⁵ and is associated with an increased risk of all-cause death.^{5–9} Consequently, this study was undertaken to examine the mode of death in patients with a recent myocardial infarction and AF, to further clarify the cause of the excess mortality observed in several studies, and to examine the risk in pre-specified subgroups.

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Methods

The study population consisted of 6676 consecutive acute myocardial infarction patients admitted to 27 centres in Denmark from May 1990 to July 1992 and screened for inclusion into the TRAndolapril Cardiac Evaluation (TRACE) study. A detailed description of this population has been reported previously.¹⁰ In brief, consecutive patients more than 18 years old were screened between days 2 and 6 after the onset of symptoms. The criteria for myocardial infarction were chest pain and/or electrocardiographic changes suggestive of infarction or ischaemia, accompanied by an increase of one or more cardiac enzymes (creatinine kinase or creatine kinase-MB or lactate dehydrogenase or lactate dehydrogenase isoenzyme 1 or aspartate aminotransferase AST) to at least twice the upper limit of the normal value at the laboratory of the participating hospital. Clinical data including presence of AF/atrial flutter (AFL) and complications during hospitalization were prospectively collected. Left ventricular systolic function was determined as wall motion index (WMI) by echocardiography.¹¹ By the use of a nine-segment model of the left ventricle, WMI was estimated using a reverse scoring system, as described by Berning *et al.*¹² WMI multiplied by 0.3 provides an estimate of left ventricular ejection fraction (LVEF). In this study, we report the estimated LVEF.

According to the available 12-lead electrocardiographic recordings and reports of monitoring, the investigators had to report whether AF/AFL was present in the following periods during hospitalization: days 1–2, days 3–4, and from day 5 until discharge from hospital. The diagnosis of AF/AFL was left at the discretion of the investigators according to the following criteria. AF: absence of P-waves, coarse or fine fibrillatory waves, and completely irregular RR-intervals; AFL: presence of regular P-waves with a rate of 250–350/min and regular or irregular RR-intervals.

Congestive heart failure (CHF) was defined as either a history of CHF requiring ongoing treatment or development of transient or permanent CHF (Killip class >1) during hospital stay. Killip class was determined daily by the local investigator during hospitalization. NYHA functional class was assessed at the time of discharge.

Survival status among all the patients screened was obtained 2 years after screening had ended and median follow-up was 32 months (interquartile range 25–40 months). Thirty-one patients were lost for follow-up and were censored in the statistical analysis when last known to be alive. Analysis of SCD and non-SCD included only events taking place after hospital discharge. Consequently, patients who died during hospitalization were removed from the present analysis, and 5983 patients discharged alive entered the analysis of this study.

The procedure for classifying SCD and non-SCD has been described previously.¹³ Briefly, SCD was defined as cardiovascular death within 1 h of onset (or significant worsening) of symptoms leading to death. An event committee classified all deaths with respect to cause and mode, using information from death certificates, police investigations, hospital records, and necropsy reports when available. First, the committee classified whether a cardiovascular disease caused death. Whenever the evidence was inadequate or uncertain, the mode of death was classified as unknown. When information was available, death was assumed to be cardiovascular unless otherwise proved. Secondly, cardiovascular death was classified as SCD or non-SCD on the basis of the time elapsed from the onset of new symptoms to death. Only cardiovascular death with a period documented to be <1 h was classified as SCD or in the case of patients found dead in bed without signs of preceding symptoms. Written informed consent was obtained before screening. The Ethics Committees of the participating hospitals approved the study.

Statistical methods

Differences between groups with respect to medical history, clinical data, and complications during hospitalization were examined through the use of χ^2 and Mann-Whitney tests for categorical and

continuous variables, respectively. Categorical variables are presented as percentages and continuous variables as median values. All tests were two-sided. A *P*-value <0.05 was considered significant. The unadjusted cause-specific mortality rates were compared with log-rank test. The associations between AF/AFL and cause-specific mortality were examined through the use of a proportional hazard multivariable regression analysis (Cox regression analysis) while adjusting for appropriate baseline characteristics. The model assumptions (proportional hazard assumption and linearity of continuous variables) were tested and found valid unless otherwise indicated. Age was the only continuous variable and linearity was tested by introducing four separate age categories and by testing if addition of three of these added significant information to the continuous age. Proportional hazards were tested by plotting the log (cumulative cause-specific hazard) against lifetime for each variable. Variables included in the multivariable analyses were age, sex, LVEF, previous myocardial infarction, CHF, angina pectoris, diabetes, hypertension, and bundle branch block. In-hospital ventricular fibrillation (VF) or ventricular tachycardia (VT) was also tested, but was not included because of insignificant association with any mode of death. Age was analysed as a continuous variable and the risk ratio was estimated for each 10-year increase in age. LVEF was dichotomized at 40% and the risk ratio was estimated for patients with LVEF <40%, using LVEF \geq 40% as the reference. Differences of influence of AF/AFL in subgroups were analysed by testing for interaction between AF/AFL and the stratifying variable.

When evaluating cause-specific mortality, the particular mode of death was defined as the event and patients experiencing any other mode of death were censored. As the Kaplan-Meier estimator is not applicable for estimating probabilities of particular modes of death in a competing risk model, such probabilities were estimated as cumulative incidence functions.¹⁴ The cumulative incidence functions were estimated from the output of the PHREG procedure, using a custom-built program.¹⁵ All event rates were estimated for the maximal length of follow-up (4 years). We also tested for interaction between AF/AFL and the aforementioned variables included in the multivariable model. All analyses were performed with the SAS system (SAS, Cary, NC, USA), version 8.2.

Results

The study population consisted of 5983 patients who were discharged alive after hospitalization for an acute myocardial infarction. Baseline characteristics are shown in *Table 1*. Sustained or paroxysmal AF/AFL was observed in 1149 patients (19%) during hospitalization.

Modes of death

During follow-up, 1659 patients (34%) died. Of these, 536 deaths were classified as SCD (11%), 725 (14%) were non-SCD, and 398 (9%) died of non-cardiovascular causes (includes 142 unclassifiable cases). The cause-specific 4-year mortality probabilities according to whether patients had AF/AFL or not are shown in *Table 2*.

Impact of AF/AFL on all-cause mortality and SCD

Figures 1 and *2* show the unadjusted all-cause mortality and SCD rate in patients with and without AF/AFL. AF/AFL was associated with an increased risk of both all-cause mortality and SCD during follow-up. Total mortality was increased by AF/AFL with a risk ratio of 1.33 (95% CI: 1.19–1.49; *P* < 0.0001) when adjustments were made for age, sex, LVEF, previous acute myocardial infarction, CHF, angina pectoris, diabetes, hypertension, and bundle branch block. With the same adjustments, the risk ratio for SCD was 1.31 (95% CI: 1.07–1.60; *P* < 0.009) (*Table 3*).

Table 1 Baseline characteristics of 5983 patients discharged alive after hospitalization for acute myocardial infarction separated in groups with and without AF/AFL during the hospital stay

	Data availability (%)	AF/AFL (n = 1149)	No AF/AFL (n = 4834)	P-value
Age (years)	100	73	66	<0.001
Male gender	100	65%	70%	<0.002
History of hypertension	99.9	25%	22%	<0.02
History of diabetes	99.9	13%	10%	<0.002
History of angina pectoris	99.9	38%	36%	0.2
Previous myocardial infarction	99.7	23%	23%	0.8
In-hospital VF	100	7%	4%	<0.001
In-hospital VT	100	16%	10%	<0.001
QRS > 120 ms	99.5	11%	6%	<0.001
LVEF	95.7	0.39	0.45	<0.001
CHF	100	69%	45%	<0.001

Table 2 The cause-specific 4-year mortality probabilities in 5983 patients discharged alive from hospital after acute myocardial infarction, separated in groups with and without AF/AFL

	AF/AFL (n = 1149) (%)	No AF/AFL (n = 4834) (%)	P-value
All deaths	482 (50)	1177 (30)	<0.001
Non-cardiovascular death	111 (12)	287 (8)	<0.001
Cardiovascular death	371 (38)	890 (22)	<0.001
Non SCD	222 (22)	503 (12)	<0.001
SCD	149 (16)	387 (10)	<0.001

Impact of AF/AFL on non-SCD

In addition to the increase in SCD, AF/AFL was associated with an increase in non-SCD. The adjusted risk ratio of AF/AFL for non-SCD death was 1.43 (95% CI: 1.21–1.70; $P < 0.0001$). This increase in risk was not significantly different from the increase in risk of SCD associated with AF/AFL. *Table 3* shows a comparison of the relative risk of AF/AFL and all other independent risk factors in our multivariable model.

Impact of the combination of AF/AFL and selected subgroups on the risk of SCD

The risk of SCD associated with AF/AFL was increased in both patients with LVEF above and below 0.40 (*Figure 3*). We did test for interaction and found a significant interaction between AF/AFL and LVEF for all-cause mortality ($P < 0.005$) but not for sudden death ($P = 0.45$). An additional analysis of the combination of AF/AFL and selected subgroups is shown in *Figures 4* and *5*. By univariable analysis, SCD was increased in all subgroups of the entire cohort of AF/AFL patients irrespective of whether or not they suffered from hypertension or diabetes or had VT/VF during hospitalization or had QRS duration ≥ 120 ms. However, the risk associated AF/AFL in patients with a QRS duration ≥ 120 ms was markedly higher than in the other subgroups. In patients with LVEF < 0.40 and AF, the risk was still increased in this subgroup and also in patients with diabetes and patients suffering from VT/VF

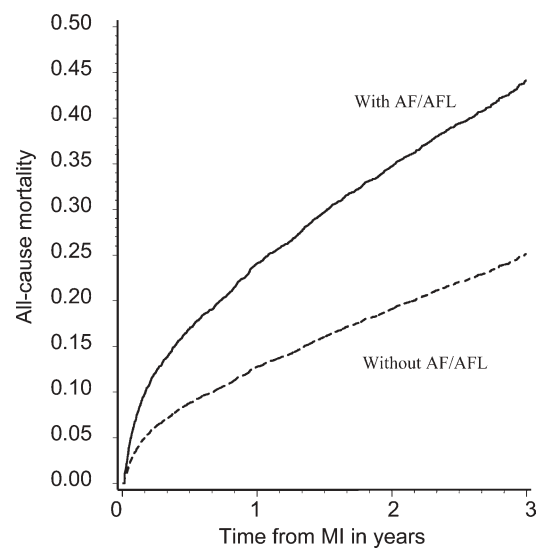
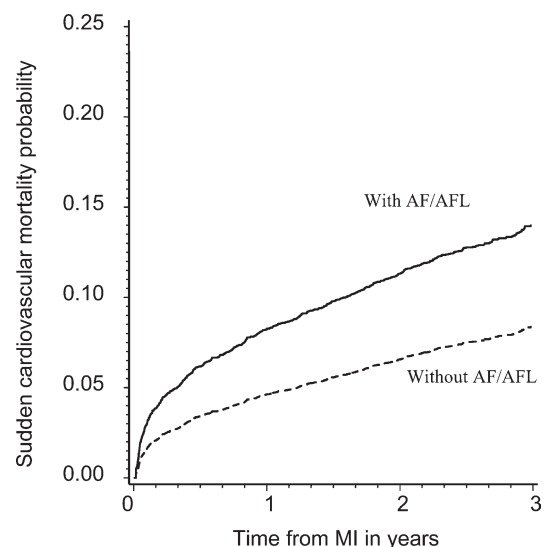
**Figure 1** The unadjusted mortality in 5983 acute myocardial infarction patients with and without AF/AFL discharged from hospital. MI, myocardial infarction.**Figure 2** The unadjusted SCD in 5983 acute myocardial infarction patients with and without AF/AFL discharged from hospital.

Table 3 A comparison of different independent risk factors for total death, SCD, and non-SCD

	Total death RR (95% CI)	P-value	SCD RR (95% CI)	P-value	Non-SCD RR (95% CI)	P-value
Age	1.60 (1.51–1.70)	0.0001	1.28 (1.67–1.41)	0.0001	1.82 (1.67–1.99)	0.0001
Sex	1.14 (1.02–1.27)	0.02	1.30 (1.07–1.59)	0.0098	1.04 (0.88–1.23)	0.64
EF	1.57 (1.41–1.75)	0.0001	1.73 (1.42–2.09)	0.0001	1.41 (1.19–1.65)	0.0001
Pre-MI	1.18 (1.05–1.32)	0.007	1.25 (1.01–1.54)	0.035	1.14 (0.95–1.36)	0.15
CHF	1.97 (1.74–2.22)	0.0001	2.12 (1.71–2.63)	0.0001	1.95 (1.62–2.36)	0.0001
Angina	1.30 (1.30–1.45)	0.0001	1.22 (1.00–1.49)	0.043	1.69 (1.41–1.98)	0.0001
Diabetes	1.50 (1.31–1.72)	0.0001	1.43 (1.12–1.82)	0.0041	1.62 (1.33–1.98)	0.0001
Hypertension	1.22 (1.09–1.37)	0.0007	1.35 (1.11–1.64)	0.0027	1.29 (1.09–1.53)	0.003
BBB	1.51 (1.30–1.76)	0.0001	1.58 (1.22–2.06)	0.0005	1.47 (1.17–1.85)	0.0009
AF/AFL	1.33 (1.19–1.49)	0.0001	1.31 (1.07–1.60)	0.009	1.43 (1.21–1.70)	0.0001

EF, ejection fraction; Pre-MI, previous myocardial infarction; BBB, bundle branch block.

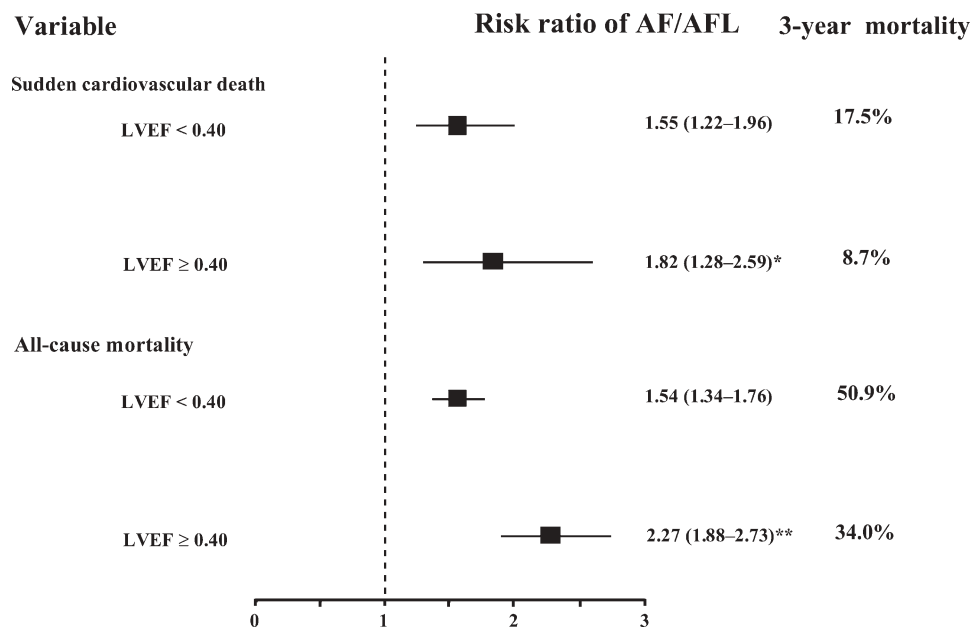


Figure 3 The univariable risk ratio associated with AF/AFL for all-cause mortality and SCD in different subgroups according to LVEF. P-value for interaction between AF/AFL and LVEF subgroup: * $P = 0.45$; ** $P < 0.005$.

during hospitalization. However, there was no significant interaction between AF/AFL and any of these subgroups.

Effect of trandolapril

Among the group of AF/AFL patients, 388 patients with AF/AFL were randomized to trandolapril ($n = 189$) or placebo ($n = 199$). Trandolapril significantly reduced total death (RR = 0.70) (95% CI: 0.51–0.95; $P < 0.05$) and cardiovascular death (RR = 0.67) (95% CI: 0.47–0.96; $P < 0.05$), but not non-SCD (RR = 0.61) (95% CI: 0.37–1.00; $P = 0.16$) or SCD (RR = 0.75) (95%CI: 0.44–1.26; $P = 0.27$).

Discussion

To our knowledge, this is the first study to examine the mode of death in patients with AF and a recent myocardial infarction as a first step to explain the excess mortality observed in this group. Our most important finding was that SCD and

non-SCD were increased to a similar extent. Therefore, the mechanism of the excess mortality is not simple and it is not related to a single aspect of the problems related to AF. Heart failure, stroke, adverse drug effects, and ventricular arrhythmias may cause AF-associated deaths. AF has been reported to facilitate induction of ventricular arrhythmia,^{16,17} and observations in patients with implantable defibrillators indicate that ventricular arrhythmias may be initiated by AF.^{18,19} By several mechanisms, AF would therefore be expected to increase the risk of sudden death. Given the multiple arrhythmic substrates in patients with a myocardial infarction, it is surprising to find that SCD was not particularly common among AF patients.

In the general population, the Framingham study has demonstrated that AF is associated with increased mortality in otherwise healthy individuals and their data did not indicate a change in mode of death.¹ In heart failure patients, the data are conflicting. In patients with severe heart failure, Middlekauff *et al.*² found that baseline AF was

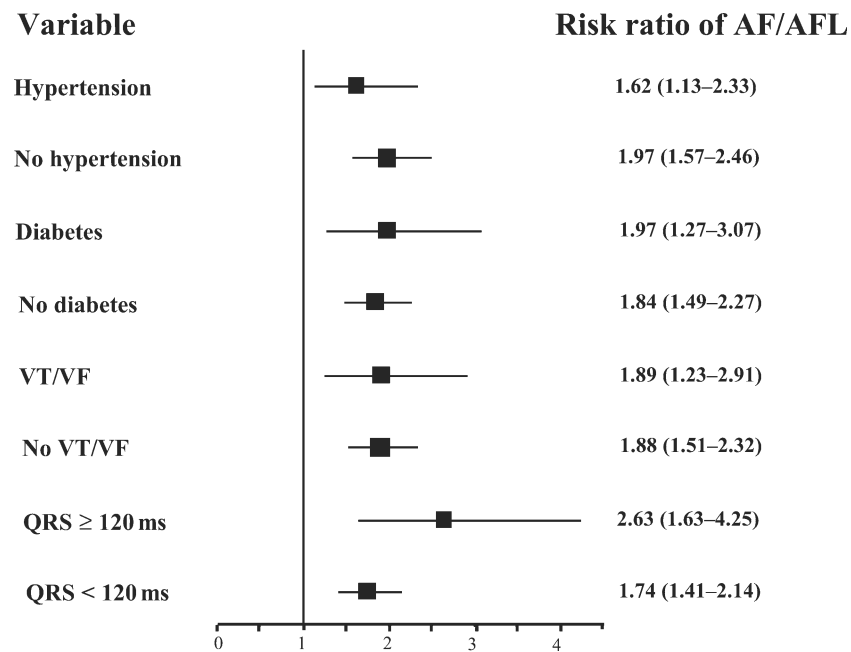


Figure 4 The univariable risk of SCD ratio associated with AF/AFL in selected subgroups in all patients.

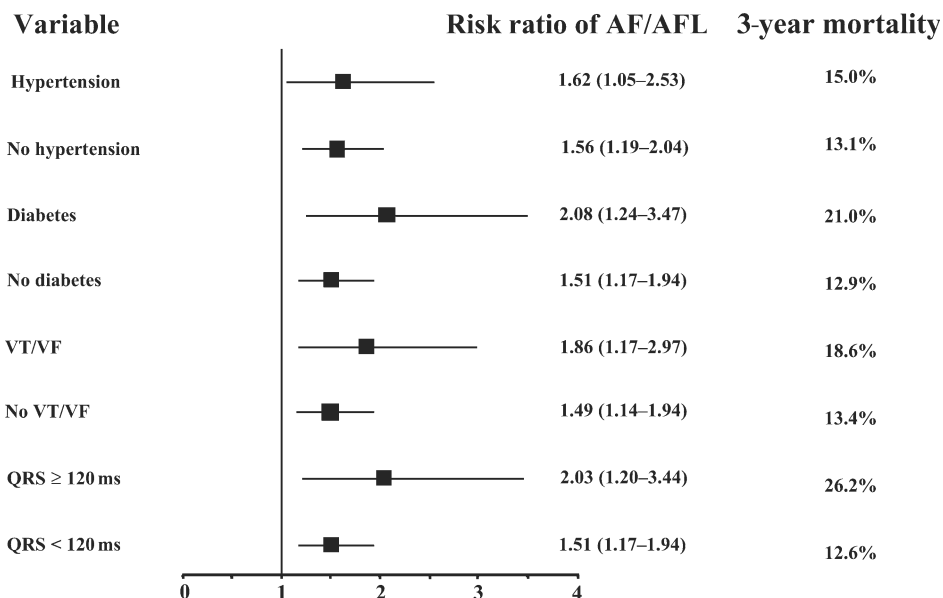


Figure 5 The univariable risk of SCD ratio associated with AF/AFL in selected subgroups in patients with LVEF < 0.40.

associated with a marked increase in SCD. Data from the Italian Network on Congestive Heart Failure Investigators also showed an increase in the risk of SCD in AF patients,²⁰ whereas Dries *et al.*²¹ and Carson *et al.*³ found that SCD was not increased in AF patients with moderate heart failure.

With this study, we wished to address whether interventions against malignant tachyarrhythmias would be likely to be particularly helpful in patients with AF. For such an analysis, it is important to note that studies, in general,

have only indicated that slightly more than half of SCD in cardiac patients are actually due to malignant ventricular arrhythmias.²² In the context of AF, this fraction could be even smaller because these patients have a high risk of stroke. Then, the risk of SCD in our study was not much higher for AF patients than for patients without AF. Thus, this study does not support the fact that myocardial infarct patients with AF are particularly likely to benefit from specific therapy against malignant ventricular arrhythmias.

We also addressed in this study whether there were likely to be subgroups with a particularly high risk of SCD in relation to AF, but we did not find any. In every subgroup analysed, SCD and non-SCD appear evenly distributed. This probably reflects that the basic disease of these patients is severe atherosclerosis and that death is related to the many manifestations of atherosclerosis, many of which can be further complicated by AF. In comparison with other studies, data from the Italian Network on Congestive Heart Failure Investigators on heart failure patients with AF in agreement with our study found bundle branch block to be a risk factor in conjunction with AF. It is of interest that SCD was increased in patients with LVEF above 40%, which is different from what would be expected from recent trials of the implantable cardioverter defibrillator (ICD).²³ Our study raises the question whether some patients with LVEF above 40%, AF, and a recent myocardial infarction could benefit from ICD therapy.

Limitations

Medical therapy of ischaemic heart disease changes rapidly and improves the prognosis after myocardial infarction. Altered prescription patterns of ACE-inhibitors, beta-blockers, anti-ischaemic, anti-coagulation drugs, and introduction of invasive treatment such as percutaneous coronary interventions since our study may have changed the risks associated with the clinical characteristics discussed in our study.

Conclusion

The excess mortality observed in patients with AF/AFL following acute myocardial infarction is due to an increase in both SCD and non-SCD.

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Conflict of interest: none declared.

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